SP-A binds to lipid A more tightly than to DPPC. These results suggest that SP-A may transfer from surfactant DPPC to pathogen membranes to initiate its host defense functions.

1294-Pos Board B245
Identifying the Choline-Cation Tyrosine-PI Interactions of an Amphitropic Protein
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Transient binding of amphitropic proteins to membranes can be mediated by phospholipid cation / tyrosine π interactions. *Bacillus thuringiensis* phosphatidylinositol-specific phospholipase C (*Bt*PI-PLC) is a secreted virulence factor that targets GPI-anchored proteins in the outer surface of eukaryotic plasma membranes, a bilayer rich in choline-containing lipids. *Bt*PI-PLC has a plethora of tyrosine residues around the surface of the α/β-barrel, and molecular dynamics (MD) simulations suggest that choline headgroups and these Tyr residues form short-lived cation-π complexes. To investigate these interactions, *Bt*PI-PLC was site-specifically spin-labeled and high resolution field cycling ^{31}P NMR relaxometry was used to quantify the effect of the spin-labeled *Bt*PI-PLC variants on phosphatidylcholine (PC) and phosphatidylmethanol (PMe, used as the surrogate substrate) in small vesicles. The paramagnetic relaxation enhancement at very low fields (<0.04 T) confirmed the existence of two moderately long-lived sites for PC binding - one near the active site and the other on the barrel rim quite removed from the active site. The distances extracted are consistent with the two major sites of PC binding suggested by the simulations. That the discrete phospholipid sites detected by NMR represent cation-π interactions is shown by measuring the binding affinity for *Bt*PI-PLC variants in which the unnatural amino acid 3,5-difluorotyrosine has been site-specifically substituted for Tyr, thus reducing the strength of cation-π interactions. These binding studies coupled with changes in enzyme activity provide a detailed and quantitative picture of how PC interactions with this PI-PLC influence its transient binding and cleavage of PI in membranes.

1295-Pos Board B246
Membrane Interaction of Amyloid-Beta Peptide Induces Spontaneous Membrane Invagination
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One of the pathological hallmarks of Alzheimer's disease (AD) is extracellular plaques, in which the 42aa Amyloid beta peptide (Aβ 1-42) is the main component. Aβ 1-42 is produced at cholesterol-rich regions of neuronal membranes by endoproteolysis of the parental amyloid precursor protein and is secreted into the extracellular space. Although Aβ 1-42 accumulates extracellularly, neurons internalize the Aβ 1-42 peptide which could contribute to disease progression and which may be the first step to both cytotoxicity and propagation of misfolded Aβ between cells.
Interaction with membrane bilayer is likely the first step in the molecular mechanism of neuronal Aβ 1-42 uptake. Therefore, we studied interaction of Aβ 1-42 with the lipid bilayer in a giant unilamellar vesicles (GUVs) model system. We found that the Aβ 1-42 bound to the lipid bilayer and, after a lag phase induced invagination of the membrane into small vesicular structures. Only early oligomeric structures of Aβ and stabilized the negative curvature of membrane, whereas both monomeric and fibrillar forms of the peptide were unable to induce or sustain membrane invagination.
Our results suggest that Aβ may facilitate vesicle formation in lipid bilayer membranes, which may be a factor in cellular Aβ internalization but may also hint at a possible physiological function of the Aβ peptide at the synaptic membrane.

1296-Pos Board B247
The Novel Inhibitor "Anle145C" Efficiently Inhibits Fibril Formation of Islet Amyloid Polypeptide (IAPP) and uses Distinctly Different Modes of Action in the Absence and Presence of Membranes
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Amyloid formation in the pancreas by islet amyloid polypeptide (IAPP) is closely associated with type-2 diabetes. Compelling evidence indicates that membranes play a crucial role in contributing to IAPP amyloid formation and that IAPP amyloid formation leads to cell membrane disruption [1]. Since both IAPP amyloid formation and membrane damage are considered perilous to the pancreatic beta-cells, their inhibition may be an effective strategy for the prevention and/ or treatment of the disease. Here, we studied the interaction between a novel amyloid inhibitor "anle145c" [2] and IAPP in the absence and presence of model membranes. Our results suggest that addition of anle145c to IAPP inhibits IAPP fibril growth even at sub-stoichiometric concentrations, both in the absence and presence of membranes. Anle145c also reduces membrane damage induced by IAPP but does not induce membrane leakage by itself. Most notably, anle145c shows a strong membrane interaction, resulting in a distinctly different mode of inhibition than in the absence of membranes. We present a model in which anle145c interacts with oligomeric IAPP species in solution, but with monomeric or early oligomeric IAPP species in the presence of membranes.
[1] Engel M et al., PNAS. (2008) - 105 :6033
[2] Wagner J et al., Acta Neuropathologica (2013) - 125: 795

1297-Pos Board B248
Influence of Sequence and Lipid Type on Membrane Perturbation by Human and Rat Amyloid β-Peptide (1-42)
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The hallmark characteristics of plaque formation and neuronal cell death in Alzheimer's disease (AD) are caused principally by the amyloid β-peptide (Aβ). Current research focuses on understanding the interactions between Aβ and neuronal cell membranes, given the relationship between membrane perturbation and neurotoxicity. Aβ sequence and lipid composition are essential variables to consider when elucidating the impact of the biological membrane on Aβ structure and the effect of Aβ on membrane integrity. Atomistic molecular dynamics simulations testing two Aβ sequences (Human $Aβ_{1-42}$) (HAβ) and Rat $Aβ_{(1-42)}$ (RAβ)), five lipid types, and totaling 9 μs in simulation time, were performed in order to explain the effect of these variables on membrane perturbation. All metrics used to assess membrane perturbation agree insomuch that it can be concluded that HAβ and RAβ contribute to membrane perturbation by causing a more rigid, gel-like lipid phase. The presence of cholesterol in a model raft membrane was found to moderate the amount of perturbation caused by HAβ and RAβ. Differences between HAβ and RAβ were seen based on lipid headgroup charge and hydrogen bond capacity. The position of arginine in the N-terminal region was determined to be the mediating factor in these differences in lipid affinity and disruption between HAβ and RAβ. Overall, this work rationalizes the influence of sequence and lipid type on Aβ-membrane interactions, providing mechanistic insight into the etiology of AD.

Membrane Receptors and Signal Transduction II

1298-Pos Board B249
Effect of Thanatophoric Dysplasia Type I Mutations on Fibroblast Growth Factor Receptor 3 Dimerization
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Thanatophoric dysplasia type I (TDI) is a lethal human skeletal growth disorder with a prevalence of 1 in 20,000 to 1 in 50,000 births. TDI is known to arise due to five different mutations, all involving the substitution of an amino acid with a cysteine in fibroblast growth factor receptor 3 (FGFR3). Cysteine mutations in receptor tyrosine kinases have been previously proposed to induce receptor cross-linking in the unliganded state, thus emulating the effect of ligand and leading to receptor overactivation. Here, we characterize the effect of three TDI mutations, Arg248Cys, Ser249Cys, and Tyr373Cys, on FGFR3 dimerization in mammalian membranes, in the absence of ligand. We demonstrate that the mutations lead to modest stabilization and structural perturbations of the FGFR3 dimers. Based on available FGFR crystal structures, we argue that the effects of these mutations cannot emulate the effect of the ligand, thus challenging the current understanding of the molecular interactions that underlie TDI.